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Stereoselective synthesis of 4-substituted azetidine-2,3-diones by ring opening of 1,3-thiazolidine-derived spiro-β-lactams

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Abstract—New 3-heterocycle substituted 1,3-thiazolidine-derived 4-spiro-β-lactams with a relative *trans*-configuration were stereoselectively synthesised by means of a *Staudinger* ketene–imine reaction between the ketene generated from the (2*S*,4*R*)-1,3-thiazolidine-2,3,4-tricarboxylic acid 3-(1,1-dimethylethyl) 4-methyl ester **1** and imines **2b**–**e**. The 1,3-thiazolidine-derived 4-spiro-β-lactams were transformed into the corresponding enantiomerically pure 4-heterocycle substituted azetidine-2,3-diones by means of an oxidative cleavage of the 1,3-thiazolidine ring. The opening of the 1,3-thiazolidine ring was studied under different experimental conditions and a consistent mechanism is proposed.

1. Introduction

The stereoselective synthesis of β-lactams has received considerable attention over recent years because of their wide variety of biological activities,[1] in particular, asymmetric synthesis by means of a *Staudinger* ketene–imine reaction has been extensively studied.[2] Spiro-β-lactams are interesting compounds not only because of their antiviral[3a] and antibacterial activities,[3b] but also because they inhibit cholesterol absorption,[3c] indicating that they are potentially useful drugs. They can also act as β-turn mimetics,[4a] while the 4-spiro-β-lactams can be used as synthetic precursors for cyclic α,α-disubstituted β-amino acids and peptide derivatives.[4b]

Some β-lactams, such as the azetidine-2,3-diones or α-keto-β-lactams, are very interesting small heterocycles that could be useful intermediates because of the various possible transformations of the ketone and amide functional groups. The most significant of these transformations involves the synthesis of 3-hydroxy substituted β-lactams, which are important key fragments of many natural products.[5]

Continuing our studies of the synthesis[6] and reactivity[7] of hetero-spirocyclic β-lactams, we have recently synthesised new 1,3-thiazolidine-derived 4-spiro-β-lactams[8a,b] using a *Staudinger* ketene–imine reaction between imines and the non-symmetrical cyclic ketenes generated from *N*-acyl-1,3-thiazolidine-2-carboxylic acids by means of *Mukaiyama*'s reagent. Subsequently, we synthesised enantiomerically pure 1,3-thiazolidine-derived 4-spiro-β-lactams **3a** and **4a** starting from the optically active (2*S*,4*R*)-1,3-thiazolidine-2,3,4-tricarboxylic acid 3-(1,1-dimethylethyl) 4-methyl ester **1** and benzyl-benzylidene-amine **2a** as indicated in Scheme 1.[8c]

Our studies led us to conclude that, when the imine-nitrogen atom is substituted with an electron-donor group (e.g., $PhCH_2$), the main diastereoisomer obtained has a relative *trans* configuration between the sulfur atom and the 3-C-phenyl group.[8b] Moreover, with the enantiomerically pure substrate **1**, the reactions afford only two diastereoisomers which have the same *trans* relative configuration but opposite configurations to the C-3 and the spiranic carbon atoms.

Our interest in compounds **3** and **4** was based on the presence of the spiro-fused 1,3-thiazolidine ring, whose selective opening made it possible to obtain α-keto-β-lactams and recover the chiral auxiliary. This transformation was accomplished in two steps: the spiro-β-lactams **3a** and **4a** were deprotected at the thiazolidine-*N*-atom under anhydrous conditions with gaseous HCl in AcOEt, and then heated in a $CHCl_3$/DMSO 90:10 solution for 6 h. These

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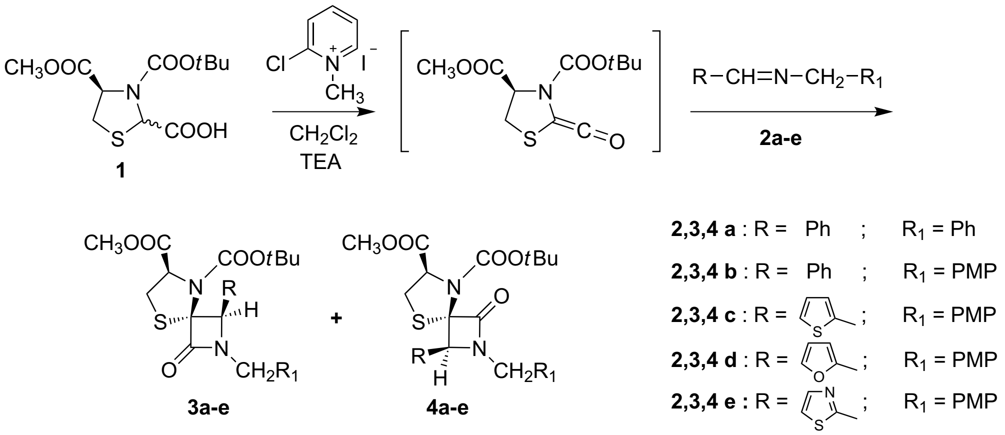

Scheme 1.

conditions allowed the corresponding α-keto-β-lactams to be obtained in good yields together with the dimethyl cystinate dihydrochloride.[8c] However, the mechanism of this reaction has not been completely clarified, and should be studied further.[8b]

In this context, and in view of the growing interest in the synthesis of enantiopure β-lactams, we herein report the asymmetric synthesis of new 1,3-thiazolidine-derived 4-spiro-β-lactams by means of a *Staudinger* ketene–imine reaction between the optically active (2*S*,4*R*)-1,3-thiazolidine-2,3,4-tricarboxylic acid 3-(1,1-dimethylethyl) 4-methyl ester **1** and imines **2b–e**, which, respectively, derive from benzaldehyde, 2-thiophene-carbaldehyde, 2-furane-carbaldehyde, 2-thiazole-carbaldehyde and 4-methoxybenzylamine. The aim was to obtain 4-spiro-β-lactams that are substituted at the 3-position by a heterocycle and have a removable group, such as the *p*-methoxy-phenyl group, on the β-lactam-nitrogen, because the transformations of these compounds would allow new azetidine-2,3-diones to be obtained. At the same time, additional studies of 1,3-thiazolidine ring opening would enable us to propose a mechanism to explain the course of the reaction.

2. Results and discussion

The starting material, (2*S*,4*R*)-1,3-thiazolidine-2,3,4-tricarboxylic acid 3-(1,1-dimethylethyl) 4-methyl ester **1**, was prepared from (*R*)-cysteine methyl ester hydrochloride and glyoxylic acid followed by treatment with $(BOC)_2O$, as previously reported.[8c] Imines **2b**,[9] **2c**, **2d** and **2e** were prepared from the corresponding aldehydes and 4-methoxybenzylamine in dry CH_2Cl_2 over anhydrous Na_2SO_4 as a single (*E*) geometrical isomer, as determined by IR and ^1H NMR. Their stability under the experimental conditions of the *Staudinger* reaction (TEA in refluxing CH_2Cl_2 for 24 h) was also confirmed by means of suitable experiments insofar as the imines were stable under these conditions (as established by ^1H NMR analysis) but, when heated in refluxing CH_3OH in the presence of CH_3ONa, they equilibrated to afford a mixture of two tautomeric imines (Fig. 1).[10]

The reaction of amino acid **1**, imines **2b–e** and 2-chloro-1-methylpyridinium iodide (*Mukaiyama*'s reagent) in the presence of TEA in refluxing CH_2Cl_2 for 24 h gave the spiro-β-lactams as a mixture of two diastereoisomers, **3b–e** and **4b–e**, which were easily separated and purified by means of flash chromatography (Scheme 1).

The relative and absolute configurations of the new stereocentres of spiro-β-lactams **3b–e** and **4b–e** were assigned by comparing the NMR spectra of the products with those of the previously obtained compounds **3a** (whose structure was confirmed by means of X-ray analysis) and **4a**.[8c] The ^1H NMR spectra were complicated by the existence of rotamers arising from the presence of the *N*-Boc group, and hence were recorded at 80 °C in DMSO-d_6. In this way, it was possible to observe a complete correspondence between the multiplicities and chemical shifts of, for example, the H-7 proton (doublet, 4.30 δ in **3a**, doublet, 4.30–4.54 δ in **3b–e**; triplet, 4.75 δ in **4a**, triplet, 4.70–4.86 δ in **4b–e**), the $COOCH_3$ signal (3.65 δ in **3a**, 3.60–3.71 δ in **3b–e**; 3.39 δ in **4a**, 3.38–3.53 δ in **4b–e**), and the H-6 protons (3.31, 3.69 δ in **3a**, 3.27–3.38, 3.50–3.70 δ in **3b–e**;

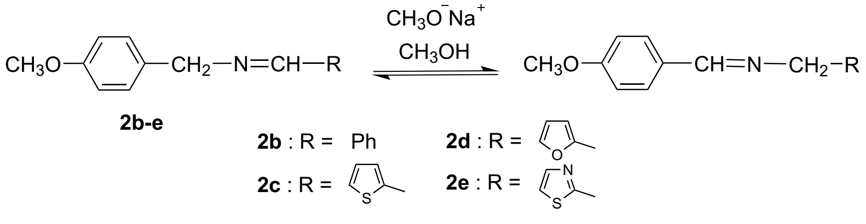

Figure 1.